Financial conflicts of interest in clinical research

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Financial conflicts of interest are common in clinical research. For example, in a cohort of oncology drug trials, industry funded 44% of trials while 69% of authors declared conflicts of interest [1]. For a drug company, the financial impact of a positive pivotal trial can be considerable. For example, the mean stock price of the companies funding 23 positive pivotal oncology trials increased by 14% after disclosure of the results [2]. Several dramatic cases of biased industry trials have been widely debated [3]. These often involved selective reporting of outcomes and gift/ghost authorships. Other cases involved companies intimidating authors of independent investigations [4].

Conflicts of interests do not necessarily cause biased trial results but create the risk thereof. Unfortunately, our knowledge of what factors affect that risk, and to what extent, is incomplete. In this editorial we address the intersection between financial conflicts of interest, including industry funding, and bias in clinical research.

A conflict of interest is typically defined as: “a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest” [5]. In clinical research, the primary interest is to conduct a relevant and unbiased investigation. Secondary interest typically relates to financial relations. Financial conflicts of interest arise when clinical investigators have relationships with the company that manufactures the drug or device subject of the investigation. Those relationships could be in the form of study funding; monetary payments, consultancies, share ownership, or advisory board membership; or when investigators stand to gain financially from a study result in other ways, e.g. patents.

Bias is a systematic error in the results of individual studies or their synthesis. Bias in this technical and narrow sense should be clearly distinguished from its broader meanings of prejudiced investigator motives, and "problematic" investigation.

When addressing the risk of bias in a clinical study it may be challenging to determine which aspects of a trial should be regarded as indicators of bias, e.g., whether conflict of interests should be considered. The widely used Cochrane risk of bias tool for randomized trials addresses this by including only six mechanistically defined core bias domains: generation of allocation sequence, concealment of allocation sequence, blinding of participants and treatment providers, blinding of outcome assessors, attrition, and publication bias. Financial conflicts of interests is not included (though this has been debated) as it is not regarded a mechanism through which biases are introduced into trials, but a motivation behind them. The intention is to pick up any bias associated with conflict of interest indirectly through one of the outlined mechanisms.

A key question is whether trials with and without financial conflicts of interests reach different results. A systematic review of 75 such comparisons reported that industry funding was associated with positive trial conclusions and more frequent statistically significant results, but could give no clear answer to whether the size of the estimated treatment effects differed, and found no association with the assessment of conventional bias domains [6]. However, confounding in such comparisons is considerable, as the result of trials may differ for many reasons other than funding source (e.g. choice of study comparator or outcome). One included study minimized this risk of confounding by sampling comparable trials from meta-analyses. It reproduced the general association with positive conclusions and no clear association with size of estimated treatment effects [7]. A similar pattern was found in studies of financial conflicts of interest in systematic reviews [8]. So, it appears that commercial funding is robustly associated with favorable conclusions but less so with estimated treatment effects.

Industry funded trials often differ from non-industry funded ones. An industry funded trial is often large, participants are often carefully selected, placebo is often used as comparator, and short-time surrogate outcomes are frequently used [9,10]. In some cases industry trials or outcomes may not be published if deemed commercially unfavorable. Trial registration and decades of debate about publication bias have improved matters to some degree, but lack of transparency and incomplete reporting of trials is still a significant problem [10,11]. Furthermore, trial results are often over-interpreted and spin in conclusions is frequent [12]. Such trials, if fully reported, may not be biased in the strict sense that their estimated treatment effect is wrong, but they are often problematic in the broader sense that results do not include the most relevant outcomes or may not be directly transferable to the typical patient.

Besides industry funding, individual and institiutional financial conflicts of interest of clinical investigators, as well as their non-financial conflicts may also unduly influence the planning, conduct and reporting of their studies. Financial ties of principal investigators seem to be independently associated with positive clinical trial results [13]. In addition, financial conflicts of interest may bias the dissemination of study findings, e.g., when these investigators display strong advocacy on social

media. Moreover, conflicted investigators may inappropriately favor industry interests when acting as content experts on panels of regulatory agencies or clinical practice guidelines [14].

The most common approach to managing conflicts of interest of clinical investigators is the public reporting of relevant conflicts. Unfortunately, there is evidence of high rates of underreporting of financial conflicts of interest [15]. In addition, there is concern that simple public disclosure, particularly in the context of guideline panels, is not enough. Problems related to conflicts of interest in trials may be especially concerning in systematic reviews where several trials are combined. To counter this, a tool to address conflicts of interest in trials (TACIT) is under development under the auspices of the Cochrane Bias Methods Group.

The field of clinical research needs to improve its approaches to identifying and managing financial conflicts of interest. This includes the need to develop methods and tools to verify the accuracy and completeness of declared financial conflicts of interest; to further assess the extent of bias associated with a financial relationship; and to minimize the risk of bias associated with the conflicts of interest of investigators.

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References

1. Riechelmann RP, Wang L, O'Carroll A, Krzyzanowska MK (2007) Disclosure of conflicts of interest by authors of clinical trials and editorials in oncology. J Clin Oncol 25(29):4642-4647.
2. Rothenstein JM, Tomlinson G, Tannock IF, Detsky AS (2011) Company stock prices before and after public announcements related to oncology drugs. J Natl Cancer Inst 103(20):1507-1512.
3. Le Noury J, Nardo JM, Healy D, et al. (2015) Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ 351(7):h4320.
4. Wojcik J (2012) Pharma giant threatens Danish scientist. Science Nordic. http://sciencenordic.com/pharma-giant-threatens-danish-scientist. Accessed 15th June 2018.
5. Lo B, Field MJ (ed) (2009) Conflict of Interest in Medical Research, Education, and Practice. Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice. National Academies Press (US), Washington (DC).
6. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L (2017) Industry sponsorship and research outcome. Cochrane Database Syst Rev 2017;2:MR000033.
7. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL (2003) Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA 290(7):921-298.
8. Hansen C, Lundh A, Rasmussen K, Frandsen TF, Gøtzsche PC, Hróbjartsson A. (2017) The Influence of Industry Funding and Other Financial Conflicts of Interest on the Outcomes and Quality of Systematic

Reviews . Eighth International Congress on Peer Review and Scientific Publication Chicago, Illinois, USA. September 10-12, 2017.
9. Mann H, Djulbegovic B (2013) Comparator bias: why comparisons must address genuine uncertainties. J R Soc Med 106(1):30-33.
10. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R (2008) Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 358:252–260.
11. Vedula SS, Bero L, Scherer RW, Dickersin K (2009) Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med 361(20):1963-1971.
12. Boutron I, Dutton S, Ravaud P, Altman DG (2010) Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. JAMA 303(20):2058-2064.
13. Ahn R, Woodbridge A, Abraham A, Saba S, Korenstein D, Madden E, Boscardin WJ, Keyhani S (2017) Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study**.** BMJ 356:i6770.
14. Lurie P, Almeida CM, Stine N, Stine AR, Wolfe SM (2006) Financial conflict of interest disclosure and voting patterns at Food and Drug Administration Drug Advisory Committee meetings. JAMA 295(16):1921-1928.
15. Okike K, Kocher MS, Wei EX, Bhandari M (2009). Accuracy of conflict-of-interest disclosures reported by physicians. N Engl J Med 361(15):1466-1474.